

maintaining the rejection, the examiner asserts that because Emilie in view of Sato teach the administration of the PM-1 antibody for the treatment of cachexia, it would be inherent in the method that it would treat the patient suffering from an elevated blood level of ionized calcium accompanied by cachexia. Applicants respectfully traverse.

None of the cited references teach or suggest the use of an antibody to an IL-6 receptor ("IL-6R") in suppressing elevation of a blood level of ionized calcium. Thus, neither Emilie nor Sato mentions the patient population that needs control of an elevated blood level of ionized calcium. Nothing in Emilie or Sato remotely suggests taking the antibody to IL-6R for reducing an ionized calcium blood level although Emilie describes abrogation of fever, sweats and cachexia as effects of administration of the antibody to IL-6R.

To make up for the lack of disclosure, the examiner seems to rely on an inherency theory. Contrary to the examiner's allegation, however, none of the disclosure in the prior art references qualifies as inherent disclosure of the suppression of elevation of a blood level of ionized calcium.

In relying upon the theory of inherency the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Applicants respectfully submit that the examiner fails to meet such a burden in this case.

The examiner has not provided any basis or technical reasoning as to how suppression of elevation of a blood level of ionized calcium of the recited antibodies to IL-6 receptor (anti-IL-6R antibody) necessarily flows from treating cachexia. In other words, there is no teaching or indication in either of Emilie or Sato that cachexia always accompanies with elevation of ionized calcium blood level, *i.e.*, hypercalcemia, or *vice versa*. Moreover, none of the prior art references teach or suggest any relation between hypercalcemia and IL-6, let alone any mention of hypercalcemia.

However, the examiner does not provide any objective evidence that a patient of cachexia necessarily suffers from hypercalcemia. Indeed, the law governing the inherent disclosure is very clear that the extrinsic evidence “must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by a person skilled in the art. Inherency, however, may not be established by probabilities or possibilities.” *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). That a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

Thus, given the lack of disclosure in the cited references, combined with the absence of any other objective evidence curing the missing description, a person of ordinary skill in the art would not infer from the cited references that the ability to suppress elevation of an ionized calcium blood level is an inherent property of the antibody to IL-6R in the prior art references

It is well accepted that the discovery of a new use for an old structure based on unknown properties of the structure is patentable as a process of using. As explained above, the use of an antibody to IL-6R for suppressing elevation of an ionized calcium blood level is not known. Thus, the claimed method is patentable over the prior art as a new use of the antibody to IL-6R, regardless of whether the combination of the Emilie and Sato would suggest the treatment of a patient of cachexia using the antibody to IL-6R.

Nonetheless, applicants wish to point out that the prior art references do not provide any motivation for one of ordinary skill in the art to modify the method of using the antibody to IL-6R with a reasonable expectation of success to obtain *in vivo* therapeutic effects of cachexia, which further buttresses the patentability of the claimed method over the prior art. The disclosure of Emilie relates to the use of an antibody to IL-6, not to an antibody to IL-6R. Applicants respectfully submit that the examiner’s finding of motivation to combine Emilie and Sato is derived from neglecting the critical difference between the antibody to IL-6 and an antibody to IL-6R in their functions.

It is known that a larger amount of IL-6 receptor is present in the blood in comparison with the amount of IL-6 (pg/ml level), which means that the amount of the antibody to IL-6R necessary to block the IL-6 signal transduction would be much greater than that of the antibody to IL-6. Thus, prior to the present invention, one of ordinary skill in the art would expect with high possibility that the antibody to IL-6R would not show the same degree of therapeutic effects as that of the antibody to IL-6. Moreover, one skilled in the art would expect a side effect of ADCC/CDC because of binding of an antibody to receptors on the cell membrane. Such a side effect would not be expected when an anti-IL-6 antibody binds to IL-6 as disclosed in Emilie because IL-6 is a soluble factor. Especially, in a condition such as cachexia, wherein the systemic condition is worsened, the side effect could develop a serious condition, and the body weight is an important indicator for the detection of the presence or absence of the side effect. Indeed, Sato cited by the examiner to show the efficacy of antibody to IL-6R in inhibiting the transduction of IL-6 is limited to *in vitro* test results, but does not disclose any evidence supporting *in vivo* efficacy of the antibody to IL-6R. Therefore, in view of the expected side effects caused by using an antibody to IL-6R, neither Emilie nor Sato evidences motivation for one of ordinary skill in the art to use the antibody to IL-6R instead of the antibody to IL-6 to provide the claimed method with a reasonable expectation of success.

In view of the above, applicants respectfully submit that the examiner fails to establish a *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

If there are any issues remaining which the examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the examiner hereby is respectfully invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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